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14. ABSTRACT

The possible role of histone deacetylase inhibitors (HDACi) in breast cancer treatment is an area of active investigation. However, its potential as a preventive agent has not been studied. Valproic acid (VPA) is an HDACi which has been used for many decades to safely treat neurological disorders. The rationale for the use of HDACi in breast cancer prevention is a previously unexplored area of research that is based on compelling preclinical data. Epidemiologic studies showing an association between HDACi use and breast cancer incidence would be important evidence to support future prospective clinical trials of HDACi in cancer prevention. **The aim of this project is to ascertain whether the risk of incident breast cancer is reduced in patients with a history of VPA use, and if so, to determine whether this effect is proportional to the duration of VPA use and whether all subtypes of breast cancer are impacted similarly.** We have developed a database using de-identified data from the Kaiser Permanente of Northern California (KPNC) clinical and pharmacy records between 1997 and 2007. 22,488 breast cancer cases and 224,860 controls have been identified. Controls have been matched to cases

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INTRODUCTION

The possible role of histone deacetylase inhibitors (HDACi) in breast cancer treatment is an area of active investigation(1-5). However, its potential as a preventive agent has not been studied. Valproic acid (VPA) is an HDACi which has been used for many decades to safely treat neurological disorders. The rationale for the use of HDACi in breast cancer prevention is a previously unexplored area of research that is based on compelling preclinical data, that shows that VPA reduces risk of invasive breast cancer in animal models(1). Epidemiologic studies showing an association between HDACi use and breast cancer incidence would be important evidence to support future prospective clinical trials of HDACi in cancer prevention. **We hypothesize that the risk of incident breast cancer is reduced in patients with a history of VPA use, and that this effect is proportional to the duration of VPA use. The Specific Aims we plan to achieve are the following: Aim 1:** We will compare the incident breast cancer rate in women with a history of valproic acid use to an age-matched cohort without VPA use, adjusting for potential confounders. We will establish whether VPA is associated with a reduced risk of breast cancer in this cohort, and whether duration of therapy impacts this risk. **Aim 2:** We will determine whether the association between VPA use and incident breast cancer differs among patient populations and tumor subtypes. If feasible, we will examine this association among different race/ethnicities as well as evaluate the tumor characteristics associated with VPA use.

May 2011 revision: Response to address deficiencies in original report

This is an addendum to the original progress report submitted for original performance end date, 9/30/10.

In the original application, the methods for achieving study aims, described in above section, involved a subcontract with the managed care system Kaiser Permanente. We followed through with generating a subcontract from UCSF to Kaiser, planned on having both collected and analyzed by Kaiser, the data described in the scope of work, which would identify women who had received valproic acid within the study parameter dates and other criteria for comparison to the incidence of breast cancer.

As addressed in the original report, below (ie, "body" section) there have been significant setbacks in data retrieval and review at the Kaiser facility. We can further clarify that this has been due to staff turnover and then prioritizing the project at a lower level due to backlog of urgent demands. The epidemiologist at Kaiser, Dr. Laurel Habel, was contacted by phone in mid-April to assess the likelihood of their performing the needed data system search, cleaning and analyzing the data and delivering some findings to UCSF within the next 3 months. At that time Dr. Habel was uncertain precisely when she could start this process and estimated possibly by June 2011. If this timeframe were to be carried out successfully it is probable that the data could be delivered and the final project report as well as manuscript for publication could be generated by 9/30/11, the end of the no-cost extension period.

Summary: Due to the above-described circumstances, at this time the only progress made on this research study involves the preliminary steps originally described in the "key research accomplishments" section below. This progress is insufficient, due to the lack of data retrieval required to be carried out according to the originally described "methods" section of the proposal and upon which "Aim 1" and "Aim 2" stated in above section are completely dependent. In this addendum to the original progress report we are describing specifically our contact with the managed care facility Kaiser with whom we have a subaward to carry out this data collection and analysis and the lead investigator at Kaiser has given her best judgment on the likelihood and timeline for delivering the needed deliverable. Until we at UCSF can receive this deliverable, upon which the entire write-up of the originally defined scope of work is based, we unfortunately have no specific data in hand and no important progress to report with the proposed scope of work.

BODY

During the past year, we have evaluated members within the Kaiser Permanente system in Northern California (KPNC), a closed system which provides and tracks all prescription medications provided to its members throughout the period of plan membership. Although initiation of data collection has been significantly hampered by an unanticipated turnover in programming personnel, progress has been made towards achieving our stated aims within the timeframe of the 1-year no-cost extension. Progress to date includes the following:

KEY RESEARCH ACCOMPLISHMENTS: Bulleted list of key research accomplishments emanating from this research.

- Identification of cases and controls: Cases status was determined as those female members identified by the KPNC Cancer Registry as having a diagnosis of invasive breast cancer with known ER status between 1997 and 2007.

- Cases were matched to controls on the basis of year of birth and duration of KPNC pharmacy coverage. 22,488 breast cancer cases and 224,960 controls have been thus identified. Among cases, 3,996 cases were found to be ER-negative, and 18,492 were ER-positive.

- VPA formulations carried by the KPNC pharmacy were identified and consisted of valproic acid, valproate sodium, and divalproex sodium. ICD-9 codes for indications for use have also been identified: epilepsy/seizure disorder (345.0-345.9/780.39), depression (296.2, 296.3, 311), and migraine (346.0=346.9).

- Use of exogenous hormones in this population has also been collected in the database.

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

Will be forthcoming upon completion of data collection and analysis. (Please see page 5 "response to address deficiencies in original report")

CONCLUSION: Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

Will be forthcoming upon completion of data collection and analysis. (Please see page 5 "response to address deficiencies in original report")

Expected outcomes and potential pitfalls: the expected number of new cancer diagnoses in this managed care population is over 2000 incident cases per year. However, the number of women taking VPA in this cohort is unknown. To determine a relative risk reduction of 30% with 80% power, and α of 0.05 and assuming an annual incidence rate of 3/1000 in this population, we will require approximately 3500 patients with a history of VPA use with a 2:1 matching of controls to cases. If the number of patients with a history of VPA is insufficient to adequately power this study (Task 1a), we will extend data collection to include other geographic catchment areas of this managed care group. Other outcome and predictor variables are known to have been collected in this data registry.

Facilities and Resources

Primary data retrieval will continue to be performed at the Division of Research at Northern California Kaiser. All other study-related activities will be conducted at the UCSF Cancer Center, which houses the research staff for the UCSF Breast Care Center. Sufficient space, computer, and IT resources exist to support the conduct of this study.

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